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A . Report Title: Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant Women Infected with HIV-1 for Maternal Health and for Reducing Perinatal HIV-1 Transmission In the United States

B. DATE Report Downloaded From the Internet: 17 Jun 98

C. Report's Point of Contact: (Name, Organization, Address, Office Symbol, & Ph #: U.S. Department of Health and Human Services

D. Currently Applicable Classification Level: Unclassified

E. Distribution Statement A: Approved for Public Release

F. The foregoing information was compiled and provided by:
DTIC-OCA, Initials: __PM__ **Preparation Date:** 17 Jun 98

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19980618 140

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

January 30, 1998 / Vol. 47 / No. RR-2

MMWR™

Recommendations and Reports

MORBIDITY AND MORTALITY WEEKLY REPORT

Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant Women Infected with HIV-1 for Maternal Health and for Reducing Perinatal HIV-1 Transmission in the United States

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
Atlanta, Georgia 30333

The *MMWR* series of publications is published by the Epidemiology Program Office, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

SUGGESTED CITATION

Centers for Disease Control and Prevention. Public Health Service task force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States. MMWR 1998;47(No. RR-2):[inclusive page numbers].

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Executive Committee and Consultants to the Public Health Service Task Force

On May 9, 1997, the Public Health Service convened a workshop to review a) the 1994 U.S. Public Health Service Task Force recommendations on use of zidovudine to reduce perinatal HIV-1 transmission; b) advances in understanding the pathogenesis of HIV-1 infection and the treatment of HIV-1 disease; and c) specific considerations regarding use of antiretroviral drugs in pregnant HIV-1–infected women and their infants. The workshop provided updated recommendations to the Public Health Service on the use of antiretroviral drugs for treatment of HIV-1 infection in pregnant women and for chemoprophylaxis to reduce perinatal HIV-1 transmission.

The following persons participated in the workshop and either served as the executive committee writing group that developed the recommendations or as consultants to the Public Health Service task force:

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Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant Women Infected with HIV-1 for Maternal Health and for Reducing Perinatal HIV-1 Transmission in the United States

Summary

These recommendations update the 1994 guidelines developed by the Public Health Service for the use of zidovudine (ZDV) to reduce the risk for perinatal human immunodeficiency virus type 1 (HIV-1) transmission. This report provides health-care providers with information for discussion with HIV-1–infected pregnant women to enable such women to make an informed decision regarding the use of antiretroviral drugs during pregnancy. Various circumstances that commonly occur in clinical practice are presented as scenarios and the factors influencing treatment considerations are highlighted in this report.*

In February 1994, the results of Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076 documented that ZDV chemoprophylaxis could reduce perinatal HIV-1 transmission by nearly 70%. Epidemiologic data have since confirmed the efficacy of ZDV for reduction of perinatal transmission and have extended this efficacy to children of women with advanced disease, low CD4+ T-lymphocyte counts, and prior ZDV therapy. Additionally, substantial advances have been made in the understanding of the pathogenesis of HIV-1 infection and in the treatment and monitoring of HIV-1 disease. These advances have resulted in changes in standard antiretroviral therapy for HIV-1–infected adults. More aggressive combination drug regimens that maximally suppress viral replication are now recommended. Although considerations associated with pregnancy may affect decisions regarding timing and choice of therapy, pregnancy is not a reason to defer standard therapy. The use of antiretroviral drugs in pregnancy requires unique considerations, including the potential need to alter dosing as a result of physiologic changes associated with pregnancy, the potential for adverse short- or long-term effects on the fetus and newborn, and the effectiveness for reducing the risk for perinatal transmission. Data to address many of these considerations are not yet available. Therefore, offering antiretroviral therapy to HIV-1–infected women during pregnancy, whether primarily to treat HIV-1 infection, to reduce perinatal transmission, or for both purposes, should be accompanied by a discussion of the known and unknown short- and long-term benefits and risks of such therapy for infected women and their infants. Standard antiretroviral therapy should be discussed with and offered to HIV-1–infected pregnant women. Additionally, to prevent perinatal transmission, ZDV chemoprophylaxis should be incorporated into the antiretroviral regimen.

*Information included in these guidelines may not represent approval by the Food and Drug Administration (FDA) or approved labeling for the particular product or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with the FDA-defined legal standards for product approval.

INTRODUCTION

In February 1994, the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076 demonstrated that a three-part regimen of zidovudine (ZDV) could reduce the risk for mother-to-child HIV-1 transmission by nearly 70% (*1*). The regimen includes oral ZDV initiated at 14–34 weeks' gestation and continued throughout pregnancy, followed by intravenous ZDV during labor and oral administration of ZDV to the infant for 6 weeks after delivery (Table 1). In August 1994, a Public Health Service (PHS) task force issued recommendations for the use of ZDV for reduction of perinatal HIV-1 transmission (*2*), and in July 1995, PHS issued recommendations for universal prenatal HIV-1 counseling and HIV-1 testing with consent for all pregnant women in the United States (*3*). In the 3 years since the results from PACTG 076 became available, epidemiologic studies in the United States and France have demonstrated dramatic decreases in perinatal transmission following incorporation of the PACTG 076 ZDV regimen into general clinical practice (*4–9*).

Since 1994, advances have been made in the understanding of the pathogenesis of HIV-1 infection and in the treatment and monitoring of HIV-1 disease. The rapidity and magnitude of viral turnover during all stages of HIV-1 infection are greater than previously recognized; plasma virions are estimated to have a mean half-life of only 6 hours (*10*). Thus, current therapeutic interventions focus on early initiation of aggressive combination antiretroviral regimens to maximally suppress viral replication, preserve immune function, and reduce the development of resistance (*11*). New, potent antiretroviral drugs that inhibit the protease enzyme of HIV-1 are now available. When a protease inhibitor is used in combination with nucleoside analogue reverse transcriptase inhibitors, plasma HIV-1 RNA levels may be reduced for prolonged periods to levels that are undetectable using current assays. Improved clinical outcome and survival have been observed in adults receiving such regimens (*12,13*). Additionally, viral load can now be more directly quantified through assays that measure HIV-1 RNA copy number; these assays have provided powerful new tools to assess disease stage, risk for progression, and the effects of therapy. These advances have led to substantial changes in the standard of treatment and monitoring for HIV-1–infected adults in the United States (*14*).

TABLE 1. Pediatric AIDS Clinical Trials Group (PACTG) 076 zidovudine (ZDV) regimen

Time of ZDV administration	Regimen
Antepartum	Oral administration of 100 mg ZDV five times daily, initiated at 14–34 weeks' gestation and continued throughout the pregnancy.
Intrapartum	During labor, intravenous administration of ZDV in a 1-hour initial dose of 2 mg/kg body weight, followed by a continuous infusion of 1 mg/kg body weight/hour until delivery.
Postpartum	Oral administration of ZDV to the newborn (ZDV syrup at 2 mg/kg body weight/dose every 6 hours) for the first 6 weeks of life, beginning at 8–12 hours after birth. (Note: intravenous dosage for infants who can not tolerate oral intake is 1.5 mg/kg body weight intravenously every 6 hours.)

Advances also have been made in the understanding of the pathogenesis of perinatal HIV-1 transmission. Most perinatal transmission likely occurs close to the time of or during childbirth (*15*). Additional data that demonstrate the short-term safety of the ZDV regimen are now available as a result of follow-up of infants and women enrolled in PACTG 076; however, recent data from studies of animals concerning the potential for transplacental carcinogenicity of ZDV affirm the need for long-term follow-up of children with antiretroviral exposure in utero (*16*).

These advances have important implications for maternal and fetal health. Health-care providers considering the use of antiretrovirals in HIV-1–infected women during pregnancy must take into account two separate but related issues: a) antiretroviral treatment of the woman's HIV infection and b) antiretroviral chemoprophylaxis to reduce the risk for perinatal HIV-1 transmission. The benefits of antiretroviral therapy in a pregnant woman must be weighed against the risk for adverse events to the woman, fetus, and newborn. Although ZDV chemoprophylaxis alone has substantially reduced the risk for perinatal transmission, when considering treatment of pregnant women with HIV infection, antiretroviral monotherapy is now considered suboptimal for treatment; combination drug therapy is the current standard of care (*14*). This report focuses on antiretroviral chemoprophylaxis for the reduction of perinatal HIV transmission and a) reviews the special considerations regarding the use of antiretroviral drugs in pregnant women, b) updates the results of PACTG 076 and related clinical trials and epidemiologic studies, c) discusses the use of HIV-1 RNA assays during pregnancy, and d) provides updated recommendations on antiretroviral chemoprophylaxis for reducing perinatal transmission.

These recommendations have been developed for use in the United States. Although perinatal HIV-1 transmission occurs worldwide, alternative strategies may be appropriate in other countries. The policies and practices in other countries regarding the use of antiretroviral drugs for reduction of perinatal HIV-1 transmission may differ from the recommendations in this report and will depend on local considerations, including availability and cost of ZDV, access to facilities for safe intravenous infusions among pregnant women during labor, and alternative interventions that may be being evaluated in that area.

BACKGROUND

Considerations Regarding the Use of Antiretroviral Drugs by HIV-1–Infected Pregnant Women and Their Infants

Treatment recommendations for pregnant women infected with HIV-1 have been based on the belief that therapies of known benefit to women should not be withheld during pregnancy unless they could adversely affect the mother, fetus, or infant and unless these adverse effects outweigh the benefit to the woman (*17*). Combination antiretroviral therapy, generally consisting of two nucleoside analogue reverse transcriptase inhibitors and a protease inhibitor, is the currently recommended standard treatment for HIV-1–infected adults who are not pregnant (*14*). Pregnancy should not preclude the use of optimal therapeutic regimens. However, recommendations regarding the choice of antiretroviral drugs for treatment of infected pregnant women

are subject to unique considerations, including a) potential changes in dosing requirements resulting from physiologic changes associated with pregnancy and b) the potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, which may not be known for many antiretroviral drugs. The decision to use any antiretroviral drug during pregnancy should be made by the woman after discussing the known and unknown benefits and risks to her and her fetus with her health-care provider.

Physiologic changes that occur during pregnancy may affect the kinetics of drug absorption, distribution, biotransformation, and elimination, thereby affecting requirements for drug dosing. During pregnancy, gastrointestinal transit time becomes prolonged; body water and fat increase throughout gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease; renal sodium reabsorption increases; and changes occur in metabolic enzyme pathways in the liver. Placental transport of drugs, compartmentalization of drugs in the embryo/fetus and placenta, biotransformation of drugs by the fetus and placenta, and elimination of drugs by the fetus also can affect drug pharmacokinetics in the pregnant woman. Additional considerations regarding drug use in pregnancy are a) the effects of the drug on the fetus and newborn, including the potential for teratogenicity, mutagenicity, or carcinogenicity and b) the pharmacokinetics and toxicity of transplacentally transferred drugs. The potential harm to the fetus from maternal ingestion of a specific drug depends not only on the drug itself, but on the dose ingested, the gestational age at exposure, the duration of exposure, the interaction with other agents to which the fetus is exposed, and, to an unknown extent, the genetic makeup of the mother and fetus.

Information about the safety of drugs in pregnancy is derived from animal toxicity data, anecdotal experience, registry data, and clinical trials. Minimal data are available regarding the pharmacokinetics and safety of antiretrovirals other than ZDV during pregnancy. In the absence of data, drug choice should be individualized and must be based on discussion with the woman and available data from preclinical and clinical testing of the individual drugs.

Preclinical data include in vitro and animal in vivo screening tests for carcinogenicity, clastogenicity/mutagenicity, and reproductive and teratogenic effects. However, the predictive value of such tests for adverse effects in humans is unknown. For example, of approximately 1,200 known animal teratogens, only about 30 are known to be teratogenic in humans (*18*). In addition to antiretroviral agents, many drugs commonly used to treat HIV-1–related illnesses may have positive findings on one or more of these screening tests. For example, acyclovir is positive on some in vitro carcinogenicity and clastogenicity assays and is associated with some fetal abnormalities in rats; however, data collected on the basis of human experience from the Acyclovir in Pregnancy Registry have indicated no increased risk for birth defects in infants with in utero exposure to acyclovir (*19*). Limited data exist regarding placental passage and long-term animal carcinogenicity for the FDA-approved antiretroviral drugs (Table 2).

Nucleoside Analogue Reverse Transcriptase Inhibitors

Of the five currently approved nucleoside analogue antiretrovirals, only ZDV and lamivudine (3TC) pharmacokinetics have been evaluated in clinical trials of pregnant humans. ZDV is well tolerated in pregnant women at recommended adult doses and

TABLE 2. Preclinical and clinical data relevant to the use of antiretrovirals in pregnancy*

Antiretroviral drug	Food and Drug Administration (FDA) pregnancy category†	Placental passage	Newborn:mother drug ratio	Long-term animal carcinogenicity studies
Nucleoside analogue reverse transcriptase inhibitors				
Zidovudine (ZDV)	C	In humans	0.85	Positive (rodent, noninvasive vaginal epithelial tumors)
Zalcitabine (ddC)	C	In rhesus monkeys	0.30–0.50	Positive (rodent, thymic lymphomas)
Didanosine (ddI)	B	In humans	0.5	Negative (no tumors, lifetime rodent study)
Stavudine (d4T)	C	In rhesus monkeys	0.76	Not completed
Lamivudine (3TC)	C	In humans	~1.0	Negative (no tumors, lifetime rodent study)
Non-nucleoside reverse transcriptase inhibitors				
Nevirapine	C	In humans	~1.0	Not completed
Delavirdine	C	Unknown	NA	Not completed
Protease inhibitors				
Indinavir	C	In rats	Substantial in rats; low in rabbits	Not completed
Ritonavir	B	In rats	Mid-term fetus: 1.15	Not completed
			Late-term fetus: 0.15–0.64	Not completed
Saquinavir	B	In rats/ rabbits	Minimal	Not completed
Nelfinavir	B	Unknown	NA	Not completed

* Information included in this table may not represent FDA approval or approved labeling for the particular product or indications in question. Specifically, the terms "safe"and "effective" may not be synonymous with the FDA-defined legal standards for product approval.

† FDA pregnancy categories:

A Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters);

B Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of pregnant women have not been conducted;

C Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus;

D Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks;

X Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

NA=not applicable.

in the full-term neonate at 2 mg/kg body weight administered orally every 6 hours, as observed in PACTG 076. No data are available regarding the pharmacokinetics of 3TC administered before 38 weeks' gestation. However, the safety and pharmacokinetics of 3TC alone or in combination with ZDV have been evaluated after administration to 20 HIV-infected pregnant women starting at 38 weeks' gestation, continuing through labor, and to their infants during the first week of life (*20,21*). The drug was well tolerated in the women at the recommended adult dose of 150 mg administered orally, twice daily and had pharmacokinetics similar to those observed in nonpregnant adults. In addition, no pharmacokinetic interaction with ZDV was observed. The drug crossed the placenta, achieving comparable serum concentrations in the woman, umbilical cord, and neonate; no short-term adverse effects were observed in the neonates. Oral clearance of 3TC in infants aged 1 week was prolonged compared with clearance in older children (0.35 L/kg/hour compared with 0.64–1.1 L/kg/hour, respectively). No data exist on 3TC pharmacokinetics in infants aged 2–6 weeks, and the exact age at which 3TC clearance begins to approximate that in older children is not known. Based on these limited data, 3TC is being evaluated in a phase III perinatal prevention trial in Africa and in combination with ZDV and other drugs in several phase I studies in the United States. In these studies, 3TC is administered to pregnant women at a dose of 150 mg of 3TC orally, twice daily and to their neonates at a dose of 2 mg/kg body weight orally, twice daily (i.e., half of the dose recommended for older children).

Prolonged, continuous high doses of ZDV administered to adult rodents have been associated with the development of noninvasive squamous epithelial vaginal tumors in 3%–12% of females (*22*). In humans, ZDV is extensively metabolized. Most ZDV excreted in the urine is in the form of glucuronide. In mice, however, high concentrations of unmetabolized ZDV are excreted in the urine. The vaginal tumors in mice may be a topical effect of chronic local ZDV exposure of the vaginal epithelium, resulting from reflux of urine containing highly concentrated ZDV from the bladder into the vagina. Consistent with this hypothesis, when 5 mg or 20 mg ZDV/mL saline was administered intravaginally to female mice, vaginal squamous cell carcinomas were observed in mice receiving the highest concentration (*22*). No increase in the incidence of tumors in other organs has been observed in other studies of ZDV conducted among adult mice and rats. High doses of zalcitabine (ddC) have been associated with the development of thymic lymphomas in rodents. Long-term animal carcinogenicity screening studies in which rodents have been administered ddI or 3TC have been negative; similar studies for stavudine (d4T) have not been completed.

Two studies evaluating the potential for transplacental carcinogenicity of ZDV in rodents have had differing results. In one study, two different regimens of high daily doses of ZDV were administered to pregnant mice during the last third of the gestation period (*16*). The doses administered were near the maximum dose beyond which lethal fetal toxicity would be observed and approximately 25 and 50 times greater than the daily dose administered to humans; however, the cumulative dose (on a per kg basis) received by the pregnant mouse was similar to the cumulative dose received by a pregnant woman undergoing 6 months of ZDV therapy. In the offspring of pregnant mice exposed to ZDV at the highest dose level, an increase in lung, liver, and female reproductive organ tumors was observed. In the second study, pregnant mice were administered one of several regimens of ZDV (*23*); doses were 1/12 to 1/50 the daily

doses received by mice in the previous study and were intended to achieve blood levels approximately threefold higher than those achieved with humans in clinical practice. No increase in the incidence of lung or liver tumors was observed in the offspring of these mice. Vaginal epithelial tumors were observed only in female offspring who had also received lifetime exposure to ZDV.

The relevance of these animal data to humans is unknown. In January 1997, an expert panel convened by the National Institutes of Health (NIH) reviewed these data and concluded that the proven benefit of ZDV in reducing the risk for perinatal transmission outweighed the hypothetical concerns of transplacental carcinogenesis raised by the study of rodents. The panel also concluded that the information regarding the theoretical risk for transplacental carcinogenesis should be discussed with all HIV-infected pregnant women in the course of counseling them on the benefits and potential risks of antiretroviral therapy during pregnancy. The panel emphasized the need for careful, long-term follow-up of all children exposed to antiretroviral drugs in utero. Neither transplacental carcinogenicity studies for any of the other available antiretroviral drugs nor long-term or transplacental animal carcinogenicity studies of combinations of antiretroviral drugs have been performed.

All of the nucleoside analogue antiretroviral drugs are classified as FDA Pregnancy Category C,* except for ddI, which is classified as Category B. Although all the nucleoside analogues cross the placenta in primates, in primate and placental perfusion studies, ddI and ddC undergo substantially less placental transfer (fetal/maternal drug ratios: 0.3–0.5) than do ZDV, d4T, and 3TC (fetal/maternal drug ratios: >0.7).

Non-nucleoside Analogue Reverse Transcriptase Inhibitors

Two non-nucleoside reverse transcriptase inhibitors have been approved by FDA—nevirapine and delavirdine. The safety and pharmacokinetics of nevirapine were evaluated in seven HIV-1–infected pregnant women and their infants (*24*). Nevirapine was administered to women as a single 200-mg oral dose at the onset of labor; the infants received a single dose of 2 mg/kg body weight when aged 2–3 days (*24*). The drug was well tolerated by the women and crossed the placenta; neonatal blood concentrations equivalent to those in the mother were achieved in the infants. No short-term adverse effects were observed in mothers or neonates. Elimination of nevirapine in pregnant women was prolonged (mean half-life: 66 hours) compared with that in nonpregnant persons (mean half-life: 45 hours following a single dose). The half-life of nevirapine was prolonged in neonates (median half-life: 36.8 hours)

*FDA pregnancy categories:

- A Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters);
- B Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of pregnant women have not been conducted;
- C Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus;
- D Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks;
- X Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

compared with what is observed in older children (mean half-life: 24.8 hours following a single dose). A single dose of nevirapine administered at age 2–3 days to neonates whose mothers received nevirapine during labor was sufficient to maintain levels associated with antiviral activity for the first week of life (*24*). On the basis of these data, a phase III perinatal transmission prevention clinical trial sponsored by the PACTG will evaluate nevirapine administered as a single 200-mg dose to women during active labor and as a single dose to their newborns aged 2–3 days in combination with standard maternal antiretroviral therapy and ZDV chemoprophylaxis. Chronic dosing with nevirapine beginning at 38 weeks' gestation is being evaluated, but data are not yet available; no data are available regarding the safety and pharmacokinetics of chronic dosing with nevirapine beginning earlier in pregnancy.

Delavirdine has not been studied in phase I pharmacokinetic and safety trials of pregnant women. In premarketing clinical studies, outcomes of seven unplanned pregnancies in which the woman was administered delavirdine were reported. Three pregnancies resulted in ectopic pregnancies, and three resulted in healthy live births. One woman who received approximately 6 weeks of treatment with delavirdine and ZDV early in the course of pregnancy gave birth to a premature infant who had a small muscular ventricular septal defect. Delavirdine is positive on at least one in vitro screening test for carcinogenic potential. Long-term and transplacental animal carcinogenicity studies are not available for delavirdine or nevirapine. Both drugs are associated with impaired fertility in rodents when administered at high doses, and delavirdine is teratogenic in rodents when high doses (i.e., approximately the dose that induces fetal toxicity) are administered during pregnancy. Ventricular septal defects were observed at doses associated with severe maternal toxicity. Both nevirapine and delavirdine are classified as FDA Pregnancy Category C.

Protease Inhibitors

Although phase I studies of several protease inhibitors (i.e., indinavir, ritonavir, nelfinavir, and saquinavir in combination with ZDV and 3TC) in pregnant infected women and their infants are ongoing in the United States, no data are available regarding drug dosage, safety, and tolerance of any of the protease inhibitors in pregnant women or in neonates. Although indinavir has substantial placental passage in mice, minimal placental passage has been observed in rabbits (Merck Research Laboratories, unpublished data). Ritonavir has had some placental passage in rats (Abbott Laboratories, unpublished data). The placental transfer of sequinavir in rats and rabbits is minimal (Hoffman-La Roche, Inc., unpublished data). Data are not available on placental passage for nelfinavir among rodents, and transplacental passage of any of the protease inhibitors in humans is unknown.

Administration of indinavir to pregnant rodents has not resulted in teratogenicity. However, treatment-related increases in the incidence of supernumerary and cervical ribs have been observed in the offspring of pregnant rodents receiving indinavir at doses comparable with those administered to humans. In pregnant rats receiving high doses of ritonavir (i.e., those associated with maternal toxicity), developmental toxicity was observed in their offspring, including decreased fetal weight, delayed skeletal ossification, wavy ribs, enlarged fontanelles, and cryptorchidism; however, in rabbits, only decreased fetal weight and viability were observed when ritonavir was

administered at maternally toxic doses. Studies of rodents have not demonstrated embryo toxicity or teratogenicity associated with saquinavir or nelfinavir.

Indinavir is associated with infrequent side effects in adults (e.g., hyperbilirubinemia and renal stones) that could be problematic for the newborn if transplacental passage occurs and the drug is administered near the time of delivery. Because of the immature hepatic metabolic enzymes in neonates, the drug would likely have a prolonged half-life and possibly exacerbate the physiologic hyperbilirubinemia observed in neonates. Additionally, because of the immature neonatal renal function and the inability of the neonate to voluntarily ensure adequate hydration, high drug concentrations and/or delayed elimination in the neonate could result in a higher risk for drug crystallization and renal stone development than the risk observed in adults. These concerns are theoretical; such side effects have not been reported. Because the half-life of indinavir in adults is short, these concerns may only be relevant if the drug is administered near the time of delivery. Saquinavir, ritonavir, and nelfinavir are classified as FDA Pregnancy Category B. Indinavir is classified as Category C.

FDA recently released a public health advisory regarding an association of the onset of diabetes mellitus, hyperglycemia, and diabetic ketoacidosis and exacerbation of existing diabetes mellitus with administration of any of the four currently available protease inhibitor antiretroviral drugs in HIV-infected persons (*25*). Pregnancy is a risk factor for hyperglycemia, and whether the use of protease inhibitors will exacerbate the risk for pregnancy-associated hyperglycemia is unknown. Health-care providers caring for HIV-infected pregnant women who are receiving protease-inhibitor therapy should be aware of the possibility of hyperglycemia and closely monitor glucose levels in these patients. Such women also should be informed how to recognize the early symptoms of hyperglycemia to ensure prompt health care if such symptoms develop.

Update on PACTG 076 Results and Other Studies Relevant to ZDV Chemoprophylaxis of Perinatal HIV-1 Transmission

In 1996, final results were reported for all 419 infants enrolled in PACTG 076. The results concur with those initially reported in 1994; the Kaplan-Meier estimated HIV transmission rate for infants who received placebo was 22.6% compared with 7.6% for those who received ZDV—a 66% reduction in risk for transmission (*26*).

The mechanism by which ZDV reduced transmission in PACTG 076 has not been fully defined. The effect of ZDV on maternal HIV-1 RNA does not fully account for the observed efficacy of ZDV in reducing transmission. Preexposure prophylaxis of the fetus or infant may be a substantial component of protection. If so, transplacental passage of antiretroviral drugs would be crucial for prevention of transmission. Additionally, in placental perfusion studies, ZDV has been metabolized into the active triphosphate within the placenta (*27,28*), which could provide additional protection against in utero transmission. This phenomenon may be unique to ZDV, because metabolism to the active triphosphate form within the placenta has not been observed in the other nucleoside analogues that have been evaluated (i.e., ddI and ddC) (*29,30*). The presence of ZDV-resistant virus was not necessarily associated with failure to prevent transmission. In a preliminary evaluation of genotypic resistance in pregnant women in PACTG 076, ZDV-resistant virus was present at delivery in only one of seven women who had transmitted virus to their newborns, had received ZDV, and had

samples that could be evaluated; this woman had ZDV-resistant virus when the study began despite having had no prior ZDV therapy (*31*). Additionally, the one woman in this evaluation in whom the virus developed genotypic resistance to ZDV during the study period did not transmit HIV-1 to her infant.

In PACTG 076, similar rates of congenital abnormalities occurred in infants with and without in utero ZDV exposure. Data from the Antiretroviral Pregnancy Registry also have demonstrated no increased risk for congenital abnormalities among infants born to women who receive ZDV antenatally compared with the general population (*32*). Data for uninfected infants from PACTG 076 followed from birth to a median age of 3.9 years have not indicated any differences in growth, neurodevelopment, or immunologic status among infants born to mothers who received ZDV compared with those born to mothers who received placebo (*33*). No malignancies have been observed in short-term (i.e., up to 6 years of age) follow-up of more than 734 infants from PACTG 076 and from a prospective cohort study involving infants with in utero ZDV exposure (*34*). However, follow-up is too limited to provide a definitive assessment of carcinogenic risk with human exposure. Long-term follow-up continues to be recommended for all infants who have received in utero ZDV exposure (or in utero exposure to any of the antiretroviral drugs).

The effect of temporary administration of ZDV during pregnancy to reduce perinatal transmission on the induction of viral resistance to ZDV and long-term maternal health requires further evaluation. Preliminary data from an interim analysis of PACTG protocol 288 (a study that followed women enrolled in PACTG 076 through 3 years postpartum) indicate no substantial differences at 18 months postpartum in CD4+ T-lymphocyte count or clinical status in women who received ZDV compared with those who received placebo (*35*). Limited data regarding the development of genotypic ZDV-resistance mutations (i.e., codons 70 and/or 215) are available from a subset of women in PACTG 076 who received ZDV (*30*). Virus from one (3%) of 36 women receiving ZDV with paired isolates from the time of study enrollment and the time of delivery developed a ZDV genotypic resistance mutation. However, the population of women in PACTG 076 had low HIV-1 RNA copy numbers, and although the risk for inducing resistance with administration of ZDV chemoprophylaxis alone for several months during pregnancy was low in this substudy, it would likely be higher in a population of women with more advanced disease and higher levels of viral replication.

The efficacy of ZDV chemoprophylaxis for reducing HIV transmission among populations of infected women with characteristics unlike those of the PACTG 076 population has been evaluated in another perinatal protocol (i.e., PACTG 185) and in prospective cohort studies. PACTG 185 enrolled pregnant women with advanced HIV-1 disease and low CD4+ T-lymphocyte counts who were receiving antiretroviral therapy; 23% had received ZDV before the current pregnancy. All women and infants received the three-part ZDV regimen combined with either infusions of hyperimmune HIV-1 immunoglobulin (HIVIG) containing high levels of antibodies to HIV-1 or standard intravenous immunoglobulin (IVIG) without HIV-1 antibodies. Because advanced maternal HIV disease has been associated with increased risk for perinatal transmission, the transmission rate in the control group was hypothesized to be 11%–15% despite the administration of ZDV. At the first interim analysis, the combined group transmission rate was only 4.8% and did not substantially differ by whether the

women received HIVIG or IVIG or by duration of ZDV use (*36*). The results of this trial confirm the efficacy of ZDV observed in PACTG 076 and extend this efficacy to women with advanced disease, low CD4+ count, and prior ZDV therapy. Rates of perinatal transmission have been documented to be as low as 3%–4% among women with HIV-1 infection who receive all three components of the ZDV regimen, including women with advanced HIV-1 disease (*6,37*).

Whether all three parts of the ZDV chemoprophylaxis regimen are necessary for prevention of transmission is not known. Data from several prospective cohort studies indicate that the antenatal component of the regimen may have efficacy similar to that observed in PACTG 076 (*37–40*). Other data emphasize the importance of the infant component of the regimen. In a retrospective case-control study of health-care workers from the United States, France, and the United Kingdom who had nosocomial exposure to HIV-1–infected blood, postexposure use of ZDV was associated with reduced odds of contracting HIV-1 (adjusted odds ratio: 0.2; 95% confidence interval [CI]=0.1–0.6) (*41*). However, in a study from North Carolina, the rate of infection in HIV-exposed infants who received only postpartum ZDV chemoprophylaxis was similar to that observed in infants who received no ZDV chemoprophylaxis (*6*).

Although no clinical trials have demonstrated that antiretroviral drugs other than ZDV are effective in reducing perinatal transmission, potent combination antiretroviral regimens that substantially suppress viral replication and improve clinical status in infected adults are now available. However, ZDV has substantially reduced perinatal transmission despite producing only a minimal (i.e., 0.24 $\log_{10}$) reduction in maternal antenatal plasma HIV-1 RNA copy number. If preexposure prophylaxis of the infant is an essential component of prevention, any antiretroviral drug with substantial placental passage could be equally effective. However, if antiretroviral activity within the placenta is needed for protection, ZDV may be unique among the available nucleoside analogue drugs. Although combination therapy has advantages for the HIV-1–infected woman's health, further research is needed before combination antiretroviral therapy is determined to have an additional advantage for reducing perinatal transmission.

Perinatal HIV-1 Transmission and Maternal HIV-1 RNA Copy Number

The correlation of HIV-1 RNA levels with risk for disease progression in nonpregnant infected adults suggests that HIV-1 RNA should be monitored during pregnancy at least as often as recommended for persons who are not pregnant (e.g., every 3–4 months or approximately once each trimester). Whether increased frequency of testing is needed during pregnancy is unclear and requires further study. Although no data indicate that pregnancy accelerates HIV-1 disease progression, longitudinal measurements of HIV-1 RNA levels during and after pregnancy have been evaluated in only one prospective cohort study. In this cohort of 198 HIV-1–infected women, plasma HIV-1 RNA levels were higher at 6 months postpartum than during antepartum in many women; this increase was observed in women regardless of ZDV use during and after pregnancy (*42*).

Data regarding the correlation of viral load with risk for perinatal transmission have been conflicting, with some studies suggesting an absolute correlation between HIV-1 RNA copy number and risk for transmission (*43*). However, although higher HIV-1

RNA levels have been observed among women who transmitted HIV-1 to their infants, overlap in HIV-1 RNA copy number has been observed in women who transmitted and those who did not transmit the virus. Transmission has been observed across the entire range of HIV-1 RNA levels (including in women with HIV-1 RNA copy number below the limit of detection of the assay), and the predictive value of RNA copy number for transmission has been relatively poor (*42,44–46*). In PACTG 076, antenatal maternal HIV-1 RNA copy number was associated with HIV-1 transmission in women receiving placebo. In women receiving ZDV, the relationship was markedly attenuated and no longer statistically significant (*26*). An HIV-1 RNA threshold below which there was no risk for transmission was not identified; ZDV was effective in reducing transmission regardless of maternal HIV-1 RNA copy number.

Although a correlation exists between plasma and genital viral load, women can have undetectable plasma HIV-1 RNA levels but detectable virus in the genital tract (*47*). If exposure to HIV in the maternal genital tract during delivery is a risk factor for perinatal transmission, then plasma HIV-1 RNA levels may not be a fully accurate indicator of risk.

Whether lowering maternal HIV-1 RNA copy number during pregnancy could reduce the risk for perinatal transmission has not been determined. Of 44 HIV-infected pregnant women, ZDV was effective in reducing transmission despite minimal effect on HIV-1 RNA levels (*48*). These results are similar to those observed in PACTG 076 (*26*). However, it is not known whether a more potent antiretroviral regimen that more substantially suppresses viral replication would be associated with enhanced efficacy in reducing the risk for transmission. Determination of HIV-1 copy number influences decisions associated with treatment. However, because ZDV is beneficial regardless of maternal HIV-1 RNA level and because transmission may occur when HIV-1 RNA is not detectable, HIV-1 RNA levels should not be the determining factor when deciding whether to use ZDV chemoprophylaxis.

GENERAL PRINCIPLES REGARDING THE USE OF ANTIRETROVIRALS IN PREGNANCY

Medical care of the HIV-1–infected pregnant woman requires coordination and communication between the HIV-specialist caring for the woman when she is not pregnant and her obstetrician. Decisions regarding the use of antiretroviral drugs during pregnancy should be made by the woman after discussion with her health-care provider about the known and unknown benefits and risks of therapy. Initial evaluation of an infected pregnant woman should include an assessment of HIV-1 disease status and recommendations regarding antiretroviral treatment or alteration of her current antiretroviral regimen. This assessment should include a) evaluation of the degree of existing immunodeficiency determined by CD4+ count, b) risk for disease progression as determined by the level of plasma RNA, c) history of prior or current antiretroviral therapy, d) gestational age, and e) supportive care needs. Decisions regarding initiation of therapy should be the same for women who are not currently receiving antiretroviral therapy and for women who are not pregnant, with the additional consideration of the potential impact of such therapy on the fetus and infant (*14*). Similarly, for women currently receiving antiretrovirals, decisions regarding alterations in therapy should involve the same parameters as those used for women

who are not pregnant. Additionally, use of the three-part ZDV chemoprophylaxis regimen, alone or in combination with other antiretrovirals, should be discussed with and offered to all infected pregnant women to reduce the risk for perinatal HIV transmission.

Decisions regarding the use and choice of antiretroviral drugs during pregnancy are complex. Several competing factors influencing risk and benefit must be weighed. Discussion regarding the use of antiretroviral drugs during pregnancy should include a) what is known and not known about the effects of such drugs on the fetus and newborn, including lack of long-term outcome data on the use of any of the available antiretroviral drugs during pregnancy; b) what is recommended in terms of treatment for the health of the HIV-1–infected woman; and c) the efficacy of ZDV for reduction of perinatal HIV transmission. Results from preclinical and animal studies and available clinical information about the use of the various antiretroviral agents during pregnancy also should be discussed. The hypothetical risks of these drugs during pregnancy should be placed in perspective to the proven benefit of antiretroviral therapy for the health of the infected woman and the benefit of ZDV chemoprophylaxis for reducing the risk for HIV-1 transmission to her infant.

Discussion of treatment options should be noncoercive, and the final decision regarding the use of antiretroviral drugs is the responsibility of the woman. Decisions regarding use and choice of antiretroviral drugs in persons who are not pregnant are becoming increasingly complicated, as the standard of care moves toward simultaneous use of multiple antiretroviral drugs to suppress viral replication below detectable limits. These decisions are further complicated in pregnancy, because the long-term consequences for the infant who has been exposed to antiretroviral drugs in utero are unknown. A decision to refuse treatment with ZDV or other drugs should not result in punitive action or denial of care. Further, use of ZDV alone should not be denied to a woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and who therefore, following counseling, chooses to receive only ZDV during pregnancy to reduce the risk for perinatal transmission.

A long-term treatment plan should be developed after discussion between the patient and the health-care provider. Such discussions should emphasize the importance of adherence to any prescribed antiretroviral regimen. Depending on individual circumstances, provision of support services, mental health services, and drug abuse treatment may be required. Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential to assist the infected woman in ensuring adherence to antiretroviral treatment regimens.

General counseling should include information regarding what is known about risk factors for perinatal transmission. Cigarette smoking, illicit drug use, and unprotected sexual intercourse with multiple partners during pregnancy have been associated with risk for perinatal HIV-1 transmission (*49–53*), and discontinuing these practices may provide nonpharmacologic interventions that might reduce this risk. In addition, PHS recommends that infected women in the United States refrain from breastfeeding to avoid postnatal transmission of HIV-1 to their infants through breast milk (*3,54*); these recommendations also should be followed by women receiving antiretroviral therapy. Passage of antiretroviral drugs into breast milk has been evaluated for only a few antiretroviral drugs. ZDV, 3TC, and nevirapine can be detected in the breast milk

of women, and ddI, d4T, and indinavir can be detected in the breast milk of lactating rats. Both the efficacy of antiretroviral therapy for the prevention of postnatal transmission of HIV-1 through breast milk and the toxicity of chronic antiretroviral exposure of the infant via breast milk are unknown.

Health-care providers who are treating HIV-1–infected pregnant women and their newborns should report cases of prenatal exposure to antiretroviral drugs (used either alone or in combination) to the Antiretroviral Pregnancy Registry. The registry collects observational, nonexperimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The registry is a collaborative project with an advisory committee of obstetric and pediatric practitioners, staff from CDC and NIH, and staff from pharmaceutical manufacturers. The registry allows the anonymity of patients, and birth outcome follow-up is obtained by registry staff from the reporting physician. Referrals should be directed to Antiretroviral Pregnancy Registry, Post Office Box 13398, Research Triangle Park, NC 27709–3398; telephone (919) 483-9437 or (800) 722-9292, ext. 38465; fax (919) 315-8981.

RECOMMENDATIONS FOR ANTIRETROVIRAL CHEMOPROPHYLAXIS TO REDUCE PERINATAL HIV TRANSMISSION

The following recommendations for the use of antiretroviral chemoprophylaxis to reduce the risk for perinatal transmission are based on various scenarios that may be commonly encountered in clinical practice (Table 3), with relevant considerations highlighted in the subsequent discussion sections. These scenarios present only recommendations, and flexibility should be exercised according to the patient's individual circumstances. In the 1994 Recommendations (*2*), six clinical scenarios were delineated based on maternal CD4+ count, gestational age, and prior antiretroviral use. Because current data indicate that the PACTG 076 ZDV regimen also is effective for women with advanced disease, low CD4+ count, and prior ZDV therapy, clinical scenarios by CD4+ count and prior ZDV use are not presented. Additionally, because current data indicate most transmission occurs near the time of or during delivery, ZDV chemoprophylaxis is recommended regardless of gestational age; thus, clinical scenarios by gestational age also are not presented.

The antenatal dosing regimen in PACTG 076 (100 mg administered orally five times daily) (Table 1) was selected on the basis of standard ZDV dosage for adults at the time of the study. However, recent data have indicated that administration of ZDV three times daily will maintain intracellular ZDV triphosphate at levels comparable with those observed with more frequent dosing (*55–57*). Comparable clinical response also has been observed in some clinical trials among persons receiving ZDV twice daily (*58–60*). Thus, the current standard ZDV dosing regimen for adults is 200 mg three times daily, or 300 mg twice daily. Because the mechanism by which ZDV reduces perinatal transmission is not known, these dosing regimens may not have equivalent efficacy to that observed in PACTG 076. However, a regimen of two- or three-times daily is expected to enhance maternal adherence.

The recommended ZDV dosage for infants was derived from pharmacokinetic studies performed among full-term infants (*61*). ZDV is primarily cleared through hepatic glucuronidation to an inactive metabolite. The glucuronidation metabolic enzyme system is immature in neonates, leading to prolonged ZDV half-life and clearance compared with older infants (ZDV half-life: 3.1 hours versus 1.9 hours; clearance: 10.9 versus 19.0 mL/minute/kg body weight, respectively). Because premature infants have even greater immaturity in hepatic metabolic function than full-term infants, further prolongation in clearance may be expected. In a study of seven premature infants who were 28–33 weeks' gestation and who received different ZDV dosing regimens, mean ZDV half-life was 6.3 hours and mean clearance was 2.8 mL/minute/kg body weight during the first 10 days of life (*62*). Appropriate ZDV dosing for premature infants has not been defined but is being evaluated in a phase I clinical trial in premature infants <34 weeks' gestation. The dosing regimen being studied is 1.5 mg/kg body weight orally or intravenously every 12 hours for the first 2 weeks of life; for infants aged 2–6 weeks, the dose is increased to 2 mg/kg body weight every 8 hours.

Because subtherapeutic dosing of antiretroviral drugs may be associated with enhanced likelihood for the development of drug resistance, women who must temporarily discontinue therapy because of pregnancy-related hyperemesis should not reinstitute therapy until sufficient time has elapsed to ensure that the drugs will be tolerated. To reduce the potential for emergence of resistance, if therapy requires temporary discontinuation for any reason during pregnancy, all drugs should be stopped and reintroduced simultaneously.

CLINICAL SCENARIOS

Scenario #1: HIV-Infected Pregnant Women Who Have Not Received Prior Antiretroviral Therapy

Recommendation

HIV-1–infected pregnant women must receive standard clinical, immunologic, and virologic evaluation. Recommendations for initiation and choice of antiretroviral therapy should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed (*14*). The three-part ZDV chemoprophylaxis regimen should be recommended for all HIV-infected pregnant women to reduce the risk for perinatal transmission. The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV infection should be a) discussed with the woman; b) recommended for infected women whose clinical, immunologic, and virologic status indicate the need for treatment; and c) offered to other infected women (although in the latter circumstance it is not known if the combination of antenatal ZDV chemoprophylaxis with other antiretroviral drugs will provide additional benefits or risks for the infant). Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10–12 weeks' gestation.

TABLE 3. Clinical scenarios and recommendations for the use of antiretroviral drugs to reduce perinatal human immunodeficiency virus (HIV) transmission

Clinical scenerio	Recommendations*
Scenario #1 HIV-infected pregnant women who have not received prior antiretroviral therapy.	HIV-1–infected pregnant women must receive standard clinical, immunologic, and virologic evaluation. Recommendations for initiation and choice of antiretroviral therapy should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed. The three-part zidovudine (ZDV) chemoprophylaxis regimen should be recommended for all HIV-infected pregnant women to reduce the risk for perinatal transmission. The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV infection should be a) discussed with the woman; b) recommended for infected women whose clinical, immunologic, and virologic status indicates the need for treatment; and c) offered to other infected women (although in the latter circumstance, it is not known if the combination of antenatal ZDV chemoprophylaxis with other antiretroviral drugs will provide additional benefits or risks for the infant). Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10–12 weeks' gestation.
Scenario #2 HIV-infected women receiving antiretroviral therapy during the current pregnancy.	HIV-1–infected women receiving antiretroviral therapy in whom pregnancy is identified after the first trimester should continue therapy. For women receiving antiretroviral therapy in whom pregnancy is recognized during the first trimester, the woman should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of resistance. If the current therapeutic regimen does not contain ZDV, the addition of ZDV or substitution of ZDV for another nucleoside analogue antiretroviral is recommended after 14 weeks' gestation. ZDV administration is recommended for the pregnant woman during the intrapartum period and for the newborn—regardless of the antepartum antiretroviral regimen.

TABLE 3. Clinical scenarios and recommendations for the use of antiretroviral drugs to reduce perinatal human immunodeficiency virus (HIV) transmission — Continued

Clinical scenerio	Recommendations*
Scenario #3 HIV-infected women in labor who have had no prior therapy.	Administration of intrapartum intravenous ZDV should be recommended along with the 6-week ZDV regimen for the newborn. In the immediate postpartum period, the woman should have appropriate assessments (e.g., CD4+ count and HIV-1 RNA copy number) to determine whether antiretroviral therapy is recommended for her own health.
Scenario #4 Infants born to mothers who have received no antiretroviral therapy during pregnancy or intrapartum.	The 6-week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn. ZDV should be initiated as soon as possible after delivery—preferably within 12–24 hours of birth. Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, the efficacy of this approach for prevention of transmission is unknown, and appropriate dosing regimens for neonates are incompletely defined. In the immediate postpartum period, the woman should undergo appropriate assessment (e.g., CD4+ count and HIV-1 RNA copy number) to determine if antiretroviral therapy is required for her own health.

*Discussion of treatment options and recommendations should be noncoercive, and the final decision regarding the use of antiretroviral drugs is the responsiblity of the woman. A decision to not accept treatment with ZDV or other drugs should not result in punitive action or denial of care. Use of ZDV should not be denied to a woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and who therefore chooses to receive only ZDV during pregnancy to reduce the risk for perinatal transmission.

Discussion

ZDV is the only drug that has been demonstrated to reduce the risk for perinatal HIV-1 transmission. When ZDV is administered in the three-part PACTG 076 regimen, perinatal transmission is reduced by approximately 70%. The mechanism by which ZDV reduces transmission is not known, and available data are insufficient to justify the substitution of any antiretroviral drug other than ZDV to reduce perinatal transmission. Therefore, if combination antiretroviral therapy is initiated during pregnancy, ZDV should be included as a component of antenatal therapy, and the intrapartum and newborn ZDV parts of the chemoprophylactic regimen should be recommended for the specific purpose of reducing perinatal transmission.

Women should be counseled that combination therapy may have substantial benefit for their own health but is of unknown benefit to the fetus. Potent combination antiretroviral regimens may provide enhanced protection against perinatal

transmission, but this benefit is not yet proven. Decisions regarding the use and choice of an antiretroviral regimen should be individualized based on discussion with the woman about a) her risk for disease progression and the risks and benefits of delaying initiation of therapy; b) potential drug toxicities and interactions with other drugs; c) the need for adherence to the prescribed drug schedule; and d) preclinical, animal, and clinical data relevant to use of the currently available antiretrovirals during pregnancy.

Because the period of organogenesis (when the fetus is most susceptible to potential teratogenic effects of drugs) is during the first 10 weeks of gestation and the risks of antiretroviral therapy during that period are unknown, women who are in the first trimester of pregnancy may wish to consider delaying initiation of therapy until after 10–12 weeks' gestation. This decision should be carefully considered and discussed between the health-care provider and the patient; such a discussion should include an assessment of the woman's health status and the benefits and risks of delaying initiation of therapy for several weeks.

Women for whom initiation of antiretroviral therapy for the treatment of their HIV infection would be considered optional (e.g., those with high CD4+ counts and low or undetectable RNA copy number) should be counseled regarding the potential benefits of standard combination therapy and should be offered such therapy, including the three-part ZDV chemoprophylaxis regimen. Some women may wish to restrict their exposure to antiretroviral drugs during pregnancy but to reduce the risk of transmitting HIV-1 to their infants; the three-part ZDV chemoprophylaxis regimen should be recommended for such women. In these circumstances, the development of resistance should be minimized by the limited viral replication in the patient and the time-limited exposure to ZDV. Because monotherapy with ZDV does not suppress HIV replication to undetectable levels, the use of ZDV chemoprophylaxis alone poses a theoretical concern that such therapy might select for ZDV-resistant viral variants—potentially limiting benefits from combination antiretroviral regimens that include ZDV. Data are insufficient to determine if such use would have adverse consequences for the infected woman during the postpartum period. In some combination antiretroviral clinical trials involving adults, patients with previous ZDV therapy experienced less benefit from combination therapy than those who had never received prior antiretroviral therapy (*63–65*). However, in these studies, the median duration of prior ZDV use was 12–20 months, and enrolled patients had more advanced disease and lower CD4+ counts than the population of women enrolled in PACTG 076 or for whom initiation of therapy would be considered optional. In one study, patients with <12 months of ZDV responded as favorably to combination therapy as those without prior ZDV therapy (*65*). In PACTG 076, the median duration of ZDV therapy was 11 weeks; the maximal duration of ZDV (begun at 14 weeks' gestation) would be 6.5 months for a full-term pregnancy.

For women initiating therapy who have more advanced disease, concerns are greater regarding development of resistance with use of ZDV alone as chemoprophylaxis during pregnancy. Factors that predict more rapid development of ZDV resistance include more advanced HIV-1 disease, low CD4+ count, high HIV-1 RNA copy number, and possibly syncytium-inducing viral phenotype (*66,67*). Therefore, women with such factors should be counseled that for their own health, therapy

with a combination antiretroviral regimen that includes ZDV for reducing transmission risk would be more optimal than use of ZDV chemoprophylaxis alone.

Scenario #2: HIV-Infected Women Receiving Antiretroviral Therapy During the Current Pregnancy

Recommendation

HIV-1–infected women receiving antiretroviral therapy in whom pregnancy is identified after the first trimester should continue therapy. For women receiving such therapy in whom pregnancy is recognized during the first trimester, the woman should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of drug resistance. If the current therapeutic regimen does not contain ZDV, the addition of ZDV or substitution of ZDV for another nucleoside analogue antiretroviral is recommended after 14 weeks' gestation. ZDV administration is recommended for the pregnant woman during the intrapartum period and for the newborn—regardless of the antepartum antiretroviral regimen.

Discussion

Women who have been receiving antiretroviral treatment for their HIV infection should continue treatment during pregnancy. Discontinuation of therapy could lead to rebound in viral load, which theoretically could result in decline in immune status and disease progression, potentially resulting in adverse consequences for both the fetus and the woman. Because the efficacy of non-ZDV–containing antiretroviral regimens for reducing perinatal transmission is unknown, ZDV should be a component of the antenatal antiretroviral treatment regimen after 14 weeks' gestation and should be administered to the pregnant woman during the intrapartum period and to the newborn. If a woman does not receive ZDV as a component of her antepartum antiretroviral regimen (e.g., because of prior history of ZDV-related severe toxicity or personal choice), ZDV should continue to be administered to the pregnant woman during the intrapartum period and to her newborn.

Some women receiving antiretroviral therapy may realize they are pregnant early in gestation, and concern for potential teratogenicity may lead some to consider temporarily stopping antiretroviral treatment until after the first trimester. Data are insufficient to support or refute the teratogenic risk of antiretroviral drugs when administered during the first 10 weeks of gestation. The decision to continue therapy during the first trimester should be carefully considered and discussed between the clinician and the pregnant woman. Such considerations include gestational age of the fetus; the woman's clinical, immunologic, and virologic status; and the known and unknown potential effects of the antiretroviral drugs on the fetus. If antiretroviral therapy is discontinued during the first trimester, all agents should be stopped and restarted simultaneously in the second trimester to avoid the development of drug resistance. No data are available to address

whether transient discontinuation of therapy is harmful for the woman and/or fetus.

The impact of prior antiretroviral exposure on the efficacy of ZDV chemoprophylaxis is unclear. Data from PACTG 185 indicate that duration of prior ZDV therapy in women with advanced HIV-1 disease, many of whom received prolonged ZDV before pregnancy, was not associated with diminished ZDV efficacy for reduction of transmission. Perinatal transmission rates were similar for women who first initiated ZDV during pregnancy and women who had received ZDV prior to pregnancy. Thus, a history of ZDV therapy before the current pregnancy should not limit recommendations for administration of ZDV chemoprophylaxis to reduce perinatal HIV transmission.

Some health-care providers might consider administration of ZDV in combination with other antiretroviral drugs to newborns of women with a history of prior antiretroviral therapy—particularly in situations where the woman is infected with HIV-1 with documented high-level ZDV resistance, has had disease progression while receiving ZDV, or has had extensive prior ZDV monotherapy. However, the efficacy of this approach is not known. The appropriate dose and short- and long-term safety for most antiretroviral agents other than ZDV are not defined for neonates. The half-lives of ZDV, 3TC, and nevirapine are prolonged during the neonatal period as a result of immature liver metabolism and renal function, requiring specific dosing adjustments when these antiretrovirals are administered to neonates. Data regarding the pharmacokinetics of other antiretroviral drugs in neonates are not yet available, although phase I neonatal studies of several other antiretrovirals are ongoing. The infected woman should be counseled regarding the theoretical benefit of combination antiretroviral drugs for the neonate, the potential risks, and what is known about appropriate dosing of the drugs in newborn infants. She should also be informed that use of antiretroviral drugs in addition to ZDV for newborn prophylaxis is of unknown efficacy for reducing risk for perinatal transmission.

Scenario #3: HIV-Infected Women in Labor Who Have Had No Prior Therapy

Recommendation

Administration of intrapartum intravenous ZDV should be recommended along with a 6-week ZDV regimen for the newborn. In the immediate postpartum period, the woman should have appropriate assessments (e.g., CD4+ count and HIV-1 RNA copy number) to determine whether antiretroviral therapy is recommended for her own health.

Discussion

Intrapartum ZDV will not prevent perinatal transmission that occurs before labor. Therefore, the efficacy of an intrapartum/newborn antiretroviral regimen for reducing perinatal transmission is likely to be less than the efficacy observed in PACTG 076. Increasing data indicate that most perinatal transmission occurs near to the time of or during delivery. Additionally, the efficacy of ZDV in reducing

perinatal transmission is not primarily related to treatment-induced reduction in maternal HIV-1 RNA copy number. The presence of systemic antiretroviral drug levels in the neonate at the time of delivery, when there is intensive exposure to HIV in maternal genital secretions, may be a critical component for reducing HIV transmission.

Minimal data exist to address the efficacy of a treatment regimen that lacks the antenatal ZDV component. An epidemiologic study from North Carolina compared perinatal transmission rates from mother-infant pairs who received different parts of the ZDV chemoprophylactic regimen (*6*). Among those pairs who received all three components, six (3%) of 188 infants became infected. Among those mothers who received intrapartum ZDV whose newborns also received ZDV, only one (6%) of 16 infants was infected.

ZDV readily crosses the placenta. Administration of the initial intravenous ZDV dose followed by continuous ZDV infusion during labor to the HIV-infected woman will provide her newborn, during passage through the birth canal, ZDV levels that are nearly equivalent to those in the mother. The initial intravenous ZDV dose ensures rapid attainment of virucidal ZDV levels in the woman and her infant; the continuous ZDV infusion ensures stable drug levels in the infant during the birth process—regardless of the duration of labor. Whether oral dosing of ZDV during labor in a regimen of 300 mg orally every 3 hours would provide equivalent infant drug exposure to intravenous ZDV administration is being evaluated. Until these data are available, the efficacy of oral intrapartum administration of ZDV can not be assumed to be equivalent to that for intravenous intrapartum ZDV.

ZDV administered both during the intrapartum period and to the newborn provides preexposure and postexposure prophylaxis to the infant. Recommendations for postexposure prophylaxis have been developed for health-care workers who have nosocomial exposure to HIV-1–infected blood (*68*). In such cases, ZDV should be administered as soon after exposure as possible, and the addition of 3TC is recommended in most cases to provide increased antiretroviral activity and presumed activity against ZDV-resistant HIV-1 strains. The addition of a protease inhibitor is recommended for persons who have had high-risk exposures. In situations in which the antenatal component of the three-part ZDV regimen has not been received, some clinicians might consider administration of ZDV in combination with other antiretroviral drugs to the newborn, analogous to nosocomial postexposure prophylaxis. However, no data address whether the addition of other antiretroviral drugs to ZDV increases the effectiveness of post-exposure prophylaxis in this situation or for nosocomial exposure. Any decision to use combination antiretroviral prophylaxis in the newborn must be accompanied by a discussion with the woman of the potential benefits and risks of such prophylaxis and to inform her that no data currently address the efficacy and safety of this approach.

Scenario #4: Infants Born to Mothers Who Have Received No Antiretroviral Therapy During Pregnancy or Intrapartum

Recommendation

The 6-week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn. ZDV should be initiated as soon as possible after delivery—preferably within 12–24 hours of birth. Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, the efficacy of this approach for prevention of transmission is unknown, and appropriate dosing regimens for neonates are incompletely defined. In the immediate postpartum period, the woman should undergo appropriate assessments (e.g., CD4+ count and HIV-1 RNA copy number) to determine if antiretroviral therapy is required for her own health.

Discussion

Definitive data are not available to address whether ZDV administered solely during the neonatal period would reduce the risk for perinatal transmission. However, data from a case-control study of postexposure prophylaxis of health-care workers who had nosocomial percutaneous exposure to blood from HIV-1–infected persons indicate that ZDV administration was associated with a 79% reduction in the risk for HIV-1 seroconversion following exposure (*41*). Postexposure prophylaxis also has prevented retroviral infection in some studies involving animals (*69–71*).

The interval for which benefit may be gained from postexposure prophylaxis is undefined, but data from studies of animals indicate that the longer the delay in institution of prophylaxis, the less likely that prevention will be observed. In most studies of animals, antiretroviral prophylaxis initiated 24–36 hours after exposure usually is not effective for preventing infection, although later administration has been associated with decreased viremia (*69–71*). In cats, ZDV treatment initiated within the first 4 days after challenge with feline leukemia virus afforded protection, whereas treatment initiated 1 week postexposure did not prevent infection (*72*). The relevance of these animal studies to prevention of perinatal HIV transmission in humans is unknown. HIV-1 infection is established in most infected infants by age 1–2 weeks. Of 271 infected infants, HIV-1 DNA polymerase chain reaction (PCR) was positive in 38% of infected infants tested within 48 hours of birth. No substantial change in diagnostic sensitivity was observed within the first week of life, but detection rose rapidly during the second week of life, reaching 93% by age 14 days (*73*). Therefore, initiation of postexposure prophylaxis after the age of 14 days likely would not be efficacious in preventing transmission because infection would already be established in most children.

When neither the antenatal nor intrapartum parts of the three-part ZDV regimen are received by the mother, administration of antiretroviral drugs to the newborn provides chemoprophylaxis only after HIV-1 exposure has already occurred. Some clinicians view this situation as analogous to nosocomial postexposure prophylaxis and may wish to provide ZDV in combination with one or more other antiretroviral

agents. Such a decision must be accompanied by a discussion with the woman of the potential benefits and risks of this approach and the lack of data to address its efficacy and safety.

RECOMMENDATIONS FOR THE MONITORING OF WOMEN AND THEIR INFANTS

Pregnant Woman and Fetus

HIV-1–infected pregnant women should be monitored according to the same standards for monitoring HIV-infected persons who are not pregnant. This monitoring should include measurement of CD4+ T-lymphocyte counts and HIV-1 RNA levels approximately every trimester (i.e., every 3–4 months) to determine a) the need for antiretroviral therapy of maternal HIV-1 disease, b) whether such therapy should be altered, and c) whether prophylaxis against *Pneumocystis carinii* pneumonia should be initiated. Changes in absolute CD4+ count during pregnancy may reflect the physiologic changes of pregnancy on hemodynamic parameters and blood volume as opposed to a long-term influence of pregnancy on CD4+ count; CD4+ percentage is likely more stable and may be a more accurate reflection of immune status during pregnancy (*74,75*). Long-range plans should be developed with the woman regarding continuity of medical care and antiretroviral therapy for her own health after the birth of her infant.

Monitoring for potential complications of the administration of antiretrovirals during pregnancy should be based on what is known about the side effects of the drugs the woman is receiving. For example, routine hematologic and liver enzyme monitoring is recommended for women receiving ZDV, and women receiving protease inhibitors should be monitored for the development of hyperglycemia. Because combination antiretroviral regimens have been used less extensively during pregnancy, more intensive monitoring may be warranted for women receiving drugs other than or in addition to ZDV.

Antepartum fetal monitoring for women who receive only ZDV chemoprophylaxis should be performed as clinically indicated, because data do not indicate that ZDV use in pregnancy is associated with increased risk for fetal complications. Less is known about the effect of combination antiretroviral therapy on the fetus during pregnancy. Thus, more intensive fetal monitoring should be considered for mothers receiving such therapy, including assessment of fetal anatomy with a level II ultrasound and continued assessment of fetal growth and well being during the third trimester.

Neonate

A complete blood count and differential should be performed on the newborn as a baseline evaluation before administration of ZDV. Anemia has been the primary complication of the 6-week ZDV regimen in the neonate; thus, repeat measurement of hemoglobin is required at a minimum after the completion of the 6-week ZDV regimen. Repeat measurement should be performed at 12 weeks of age, by which time any ZDV-related hematologic toxicity should be resolved. Infants who have anemia at birth or who are born prematurely warrant more intensive monitoring.

Data are limited concerning potential toxicities in infants whose mothers have received combination antiretroviral therapy. More intensive monitoring of hematologic and serum chemistry measurements during the first few weeks of life is advised in these infants.

To prevent *P. carinii* pneumonia, all infants born to HIV-1–infected women should begin prophylaxis at 6 weeks of age, following completion of the ZDV prophylaxis regimen (*76*). Monitoring and diagnostic evaluation of HIV-1–exposed infants should follow current standards of care (*77*). Data do not indicate any delay in HIV-1 diagnosis in infants who have received the ZDV regimen (*1,78*). However, the effect of combination antiretroviral therapy in the mother and/or newborn on the sensitivity of infant virologic diagnostic testing is unknown. Infants with negative virologic tests during the first 6 weeks of life should have diagnostic evaluation repeated after completion of the neonatal antiretroviral prophylaxis regimen.

Postpartum Follow-Up of Women

Comprehensive care and support services are required for HIV-1–infected women and their families. Components of comprehensive care include the following medical and supportive care services: a) primary, obstetric, and HIV specialty care; b) family planning services; c) mental health services; d) drug-abuse treatment; and e) coordination of care through case management for the woman, her children, and other family members. Support services include case management, child care, respite care, assistance with basic life needs (e.g., housing, food, and transportation), and legal and advocacy services. This care should begin before pregnancy and should be continued throughout pregnancy and postpartum.

Maternal medical services during the postpartum period must be coordinated between obstetricians and HIV specialists. Continuity of antiretroviral treatment when such treatment is required for the woman's HIV infection is especially critical and must be ensured. All women should receive comprehensive health-care services that continue after pregnancy for their own medical care and for assistance with family planning and contraception.

Data from PACTG Protocols 076 and 288 do not indicate adverse effects through 18 months postpartum among women who received ZDV during pregnancy; however, continued clinical, immunologic, and virologic follow-up of these women is ongoing. Women who have received only ZDV chemoprophylaxis during pregnancy should receive appropriate evaluation to determine the need for antiretroviral therapy during the postpartum period.

Long-Term Follow-Up of Infants

Data remain insufficient to address the effect that exposure to ZDV or other antiretroviral agents in utero might have on long-term risk for neoplasia or organ-system toxicities in children. Data from follow-up of PACTG 076 infants from birth through age 18–36 months do not indicate any differences in immunologic, neurologic, and growth parameters between infants who were exposed to the ZDV regimen and those who received placebo. Continued intensive follow-up through PACTG 219 is ongoing. PACTG 219 also will provide intensive follow-up for infants born to women who receive other antiretroviral drugs as part of PACTG perinatal protocols. Thus, some data

regarding follow-up of exposure to other antiretroviral agents alone or in combination will be available in the future.

Innovative methods are needed to provide follow-up to infants with in utero exposure to ZDV or any other antiretrovirals. Information regarding such exposure should be part of the ongoing medical record of the child—particularly for uninfected children. Follow-up of children with antiretroviral exposure should continue into adulthood because of the theoretical concerns regarding potential for carcinogenicity of the nucleoside analogue antiretroviral drugs. Long-term follow-up should include yearly physical examination of all children exposed to antiretrovirals and for older adolescent females, gynecologic evaluation with pap smears.

On a population basis, HIV-1 surveillance databases from states that require HIV-1 reporting provide an opportunity to collect information concerning in utero antiretroviral exposure. To the extent permitted by federal law and regulations, data from these confidential registries can be used to compare with information from birth defect and cancer registries to identify potential adverse outcomes.

FUTURE RESEARCH NEEDS

An increasing number of HIV-1–infected women will be receiving antiretroviral therapy for their own health during pregnancy. Preclinical evaluations of antiretroviral drugs for potential pregnancy- and fetal-related toxicities should be completed for all existing and new antiretroviral drugs. More data are needed regarding the safety and pharmacokinetics of antiretroviral drugs in pregnant women and in their neonates, particularly when they are used in combination regimens. Results from several phase I studies will be available in the next year; these results will assist in delineating appropriate dosing and will provide data regarding short-term safety of these drugs in pregnant women and their infants. However, the long-term consequences of in utero antiretroviral exposure for the infant are unknown, and mechanisms must be developed to gather information about the long-term outcome for exposed infants. Innovative methods are needed to enable identification and follow-up of populations of children exposed to antiretroviral drugs in utero. Additional studies are needed to determine the long-term consequences of transient use of ZDV chemoprophylaxis during pregnancy for women who do not choose to receive combination therapy antenatally, including the risk for development of ZDV-resistance.

Although more potent antiretroviral combination regimens that dramatically diminish viral load also may theoretically prevent perinatal transmission, no data are available to support this hypothesis. The efficacy of combination antiretroviral therapy to decrease the risk for perinatal HIV-1 transmission needs to be evaluated in ongoing perinatal clinical trials. Additionally, epidemiologic studies and clinical trials are needed to delineate the relative efficacy of the various components of the three-part ZDV chemoprophylactic regimen. Improved understanding of the factors associated with perinatal HIV transmission despite ZDV chemoprophylaxis is needed to develop alternative effective regimens. Because of the dramatic decline in perinatal HIV-1 transmission with widespread implementation of ZDV chemoprophylaxis, an international, collaborative effort is required in the conduct of such epidemiologic studies and clinical trials.

Regimens that are more feasible for implementation in less developed areas of the world are needed. The three-part ZDV chemoprophylactic regimen is complex and may not be a feasible option in many developing countries for the following reasons: a) most pregnant women seek health care only near the time of delivery, b) widespread safe administration of intravenous ZDV infusions during labor may not be possible, and c) the cost of the regimen may be prohibitive and many times greater than the per capita health expenditures for the country. Several studies are ongoing in developing countries that are evaluating the efficacy of more practical, abbreviated modifications of the ZDV regimen. Additionally, several nonantiretroviral interventions also are being studied. Results of these studies will be available in the next few years.

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